CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-982
20-936/S-008

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

K1.1A

N20982

REC.
2/15/02
2:22 PM

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets 12.5 and 25 mg For Panic Disorder

Approval Package

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B. Action Letter (AP letter)

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MEMORANDUM

DATE: February 14, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982 & NDA 20-936/S-008

SUBJECT: Addendum to My 2/12/02 memo

In my 2/12/02 memo to NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR in patients with Panic Disorder, I stated that the issue of dissolution specifications, mentioned in our Approvable letter of 1/3/00, was not addressed in any of the reviews.

I was wrong on this point. In fact, Dr. Gurpreet Gill-Sangha, the chemistry reviewer, in her comprehensive CMC review dated 2/6/02, definitively dealt with this issue (page 8).

This memo is being written to correct the record.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
2/14/02 08:23:11 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: February 12, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982 & NDA 20-936/S-008

SUBJECT: Action Memo for NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 mg and 25 mg Tablets in patients with Panic Disorder

NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 mg and 25 mg Tablets in patients with Panic Disorder, were submitted by GlaxoSmithKline on 4/22/98 and 1/25/02, respectively. NDA 20-982 was the subject of Approvable letters dated 3/10/99 and 1/3/00 (NDA 20-936/S-008 was submitted for administrative purposes only). The 1/3/00 Approvable letter requested labeling, a safety update, regulatory status and literature updates, and the adoption of certain specific dissolution specifications.

The sponsor responded to the 1/3/00 Approvable letter in a submission dated 12/18/01. This submission has been reviewed by Dr. Greg Dubitsky, medical officer, Dr. Tom Laughren, Psychiatric Drugs Team Leader, and Dr. Gurpreet Gill-Sangha, chemist. The review team recommends that the application be approved.

I agree. I have only one minor administrative point for the file.

As noted above, the 1/3/00 Approvable letter asked the sponsor to adopt specific dissolution specifications, and this issue is not addressed in the reviews. In fact, slightly modified dissolution specifications were adopted in an Approval letter dated 12/6/00 sent to NDA 20-936/S-005. This supplemental NDA was for the introduction of a new dosage strength CR tablet, 37.5 mg. This dissolution specification had previously been approved for the 12.5 and 25 mg tablets. The 12/6/00 Approval letter to NDA 20-936/S-005 definitively addressed the request in the 1/3/00 Approvable letter to NDA 20-982. Indeed, while the applications currently under consideration were submitted only for the 12.5 and 25 mg tablets, this action will include the 37.5 mg tablet as well.

For this reason, I will issue the attached Approval letter with appended labeling.

Russell Katz, M.D.

APPEARS THIS WAY
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
2/12/02 10:56:11 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 8, 2002

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Paxil CR (paroxetine controlled release tablets) for the treatment of panic disorder

TO: File NDA 20-982
[**Note:** This overview should be filed with the 12-18-01 response to the approvable action.]

This NDA was originally submitted 4-22-98, and an initial approvable letter was issued on 3-10-99. SKB responded with a 7-7-99 submission, including alternative labeling. They indicated that, as of that time, there were no new relevant clinical data to report, no foreign regulatory actions had been taken, and there were no relevant safety findings from the published literature. For completeness, they did report on the safety experience from 2 completed bioequivalence studies. The clinical information in that response was reviewed by Dr. Dubitsky (see 8-2-99 review), and we faxed the sponsor a slightly modified version of labeling on 8-17-99. Of note, we accepted most of the sponsor's proposed changes, and our disagreements were, in my view, minor. Apparently, our suggestion to delete certain terms from the Other Events table led to an extensive effort on the part of SKB to modify this section of Adverse Reactions, and when they had still not responded to our attempts to negotiate final labeling as the action date approached, we issued a second approvable letter on 1-3-00. That letter contained the same version of labeling we had faxed to the sponsor on 8-17-99, and in other respects was similar to the original approvable letter sent 3-10-99.

The sponsor finally responded to the 1-3-00 approvable letter with a 12-18-01 submission that included revised labeling, and statements in response to our requests for safety, regulatory status, and literature updates essentially indicating that there was nothing to report. The labeling included fairly minor changes relative to our 1-3-00 labeling, but did also include a number of changes that had been implemented in the intervening 2 years. Dr. Dubitsky has reviewed the revised labeling and negotiated final labeling regarding the few minor changes the sponsor had proposed (see his 1-11-02 review). I agree with this mutually agreed upon labeling, and, in my view, this NDA can now be approved.

cc:
Orig NDA 20-982 (Paxil CR/Panic Disorder)
HFD-120/Div File
HFD-120/TLaughren/RKatz/GDubitsky/MShin

DOC: MEMPXRPD.AP1

Shin, Melaine M

From: Dubitsky, Gregory M
Sent: Wednesday, February 06, 2002 10:52 AM
To: Shin, Melaine M
Cc: Laughren, Thomas P
Subject: NDA 20-982: Paxil CR for Panic Labeling

Hi Melaine,

The minor edits suggested by GSK look fine to me. So, it appears that we have reached agreement on labeling.

Attached is the final version of labeling. I have included a copy with shading to indicate additions to the approvable labeling (in case Tom wants to see these).

Thanks,

Greg

[redacted]
PAXILCR PAN
AP3.DOC

[redacted]
Shaded PAXILCR PAN
AP3.DOC

APPEARS THIS WAY
ON ORIGINAL

Shin, Melaine M

From: Susan.Weill@gsk.com
Sent: Thursday, January 31, 2002 3:42 PM
To: SHINM@cder.fda.gov
Subject: RE: Paxil CR (Panic) Adverse Event Labeling

Hi Melaine-
Sorry this was not addressed in the e-mail below.
Please refer to the fax cover of January 29, 2002, wherein we agreed to add "vasculitic syndromes (such as Henoch Schonlein purpura)" to the Postmarketing Reports section.
Thanks and apologies for the omission

Susan Weill
GlaxoSmithKline
U.S. Regulatory Affairs
610-917-6223 (phone)

"Shin, Melaine M" <SHINM@cder.fda.gov>

31-Jan-2002 15:20

To: "'Susan.Weill

cc:
Subject: RE: Paxil CR (Panic) Adverse Event Labeling

Hi Susan,

Do you also agree that we will add "vasculitic syndromes (such as Henoch Schonlein purpura)" to the Postmarketing Reports section since it wasn't mention in this e-mail.
Thanks,
Melaine

-----Original Message-----
From: Susan.Weill@sbphrd.com (mailto:Susan.Weill@sbphrd.com)
Sent: Thursday, January 31, 2002 3:04 PM
To: shinm@cder.fda.gov
Subject: FW: Paxil CR (Panic) Adverse Event Labeling

Hi Melaine-
Please see our comments below in bold font. Please let us know if you would also like a revised PI at this time.
Should you have any questions, I may be reached at 610-917-6223.
Thanks

Susan Weill
GlaxoSmithKline
U.S. Regulatory Affairs
610-917-6223 (phone)

	"Shin, Melaine M" <SHINM@cder.fda.gov> 30-Jan-2002 14:03	To: "'Susan.Weill cc: "Shin, Melaine M" Subject: FW: Paxil CR (Panic) Adverse Event Labeling

Hi Susan,

The following is the response from the Medical Officer for your earler faxed information. Please let me know if this proposal is acceptable. Also, I would appreciate your response to my earlier e-mail regarding CMC issues.
thanks,
Melaine

> -----Original Message-----
> From: Dubitsky, Gregory
> Sent: Wednesday, January 30, 2002 1:58 PM
> To: Shin, Melaine M
> Cc: Laughren, Thomas P
> Subject: Paxil CR (Panic) Adverse Event Labeling
>
> Hello Melaine,
>
> I have reviewed the FAX from GSK RE: the "Other Events" section of
> labeling for the Paxil CR for Panic NDA (20-982). Please inform the
> sponsor of the following proposal:
>
> 1) Regarding CNS Stimulation, over half of the verbatim terms subsumed by
> this COSTART term were "irritability" once akathisia was removed (see #2
> below). Hence, I recommend replacing CNS stimulation with
> "irritability." This will require a rewording of the preface to this
> section to indicate that some vague COSTART terms were replaced with more
> specific terms. Specifically, in the third paragraph of the preface, the
> phrase "those reported in terms so general as to be uninformative" in the
> third sentence should be removed. Then, the following should be added as
> the fourth sentence: "If the COSTART term for an event was so general as
> to be uninformative, it was deleted or, when possible, replaced with a
> more informative term."

Agree to replacement of "CNS Stimulation" with "Irritability". Also agree to the changes in the preface.

> 2) Akathisia should be subsumed by the term akathisia, not CNS

> stimulation. Given 6 reports of akathisia and a denominator of 760,
> akathisia should be added under Nervous System as an infrequent event.
>

"Akathisia" will replace the term"CNS Stimulation" and be added to the Other Events Observed During the Clinical Development of Paroxetine:Nervous System under the subcategory "also observed". Please note that per the algorithm used in this section of Adverse Events (described in paragraph 5 under this section) that for events that occurred with the IR product in clinical studies of depression, OCD, Panic, SAD and GAD labeling that frequencies are not listed. The subject events are for premarketing IR studies and thus fall into this "also observed" category. For clarity the revised section would read:

Nervous System: Infrequent were amnesia, ataxia, convulsion (Note: CR preferred term; moved from below), diplopia, dystonia, emotional lability, hallucinations, hypesthesia, hypokinesia, incoordination, neuralgia, neuropathy, nystagmus, paralysis, paranoid reaction, vertigo, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, , delirium, delusions, dysarthria, dyskinesia, euphoria, ex! trapyramidal syndrome, fasciculations, grand mal convulsion, hostility, hyperalgesia, i! rritability, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis [b], trismus.

> 3) With respect to no specific verbatim term
> predominated. The variety of verbatim terms suggests no specific meaning
> that can generally be ascribed to this term. Thus, this term should be
> deleted.

Agree to delete

>
> 4) Regarding most of the verbatim terms fall under
> the rubric of an experience of tightness in the throat (i.e., throat
> tightness, lump in throat, throat constriction). Thus, this term should
> be replaced with "throat tightness."

Agree to replace ." with "throat tightness"

(IMAGE)

Table of Contents
NDA 20-982
Paxil® CR (paroxetine hydrochloride)
Controlled-Release Tablets 12.5 and 25 mg
For Panic Disorder

Approvable Package

MEMORANDUM

DATE: March 8, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982

SUBJECT: Approvable Memo for NDA 20-982 for Paxil CR in Patients with Panic Attacks

On 4/22/98, SmithKline Beecham submitted NDA 20-982 for the use of Paxil CR for the treatment of patients with panic attacks. Paxil immediate release is approved for depression, OCD, and panic. Paxil CR is approved for depression. Both dosage forms are approved for once a day dosing.

The current supplement contains the results of 3 controlled trials of essentially identical design, in which patients were randomized to drug or placebo, and dosed according to a variable schedule in which doses started at 12.5 mg once a day, and could be titrated to a maximum daily single dose of 75 mg. Double blind treatment lasted for 10 weeks. The protocol specified primary outcome was a comparison of the proportion of patients in each group who had no full panic episodes during the last 2 weeks of double blind treatment. Other important variables included the median change from baseline in number of panic episodes and median change from baseline in CGI.

The data have been reviewed in detail by Dr. Dubitsky, medical officer (review dated 2/1/99) and Dr. Koti, statistician (review dated 2/25/99), and Dr. Laughren, Psychiatric Drugs Team Leader, has completed a summary of the pertinent findings. They all recommend that the application is approvable.

In brief, as Dr. Laughren describes, Study 494 yielded a clearly significant outcome on the primary analysis, and on analysis of the change from baseline in CGI. The analysis of the change from baseline in number of full panic attacks did not reach statistical significance, but was nearly so (p=0.08 for the LOCF analysis).

In Study 495, the LOCF analysis of the primary outcome was clearly not significant though numerically in favor of drug (p=0.26), but the OC analysis reached significance. Analysis of the change in number of attacks was clearly significant, as was the change from baseline in CGI.

Study 497 yielded no statistically significant outcomes on any of the 3 variables of interest.

Dr. Larry Davis contributed patients to Studies 494 and 495, but because there was a treatment by center interaction in Study 495 which was largely due to Dr. Davis' data, the

results described above were obtained with Dr. Davis' data removed. Specifically, in Study 495, he enrolled 16 Paxil patients and 15 placebo patients. All of the Paxil patients had 0 attacks, while none of the placebo patients were attack free. Because the same pattern was seen in his patients for Study 494, (although he enrolled only 4 Paxil and 3 placebo patients), his data was removed from the analysis of this study as well. Dr. Koti performed an analysis of the primary outcome in Study 495 with Dr. Davis' patient data included; it was highly statistically significant.

No important safety issues were identified in this application.

COMMENTS

The sponsor has submitted the results of 3 controlled trials, adequate by design, to establish the effectiveness of Paxil CR as a treatment for panic attacks. One of the trials provides clear support for effectiveness; a second trial (Study 495) is largely supportive, and Study 497 clearly is not.

As Dr. Laughren discusses, a single controlled trial yielding significance would have been considered sufficient to establish the effectiveness of Paxil CR as a treatment for patients with panic attacks, given the approval of the immediate release Paxil for the same indication (and given the relatively similar kinetics of the 2 products, which permit once a day dosing with both). The existence of other trials has the potential to complicate the matter, though, particularly given the less than consistent results seen. However, I agree with the review team that the data are sufficient to establish substantial evidence of effectiveness of Paxil CR in the treatment of panic attacks. Study 495 is essentially a "positive" study (indeed, if a strict Bonferroni correction were applied to the p-values obtained for the change from baseline in number of attacks and CGI, they would still reach statistical significance). It is not clear why Study 497 is clearly not positive, but the positive results for the other 2 studies establish, in my view, the effectiveness of the treatment.

Both Drs. Laughren and Dubitsky agree that it is appropriate for labeling to contain a statement describing the results of a study with the immediate release product demonstrating long term control of patients with panic attacks, because they believe that this result can reasonably be extrapolated to the CR preparation. I believe that this conclusion is based on the view that the different kinetics of the CR compared to the IR will not have a substantive effect on the effectiveness of the treatment in the long term, given that the CR is effective over a 10 week period, and, in any event, the kinetics are not extremely different (again, they are both dosed once a day). I am not completely convinced that long term control can be extrapolated from the IR data, because the difference in kinetics could possibly effect long term response, but the statement proposed makes clear that the prescriber should periodically reevaluate the long term usefulness of the CR. I agree, then, that the proposed statement is reasonable.

For the reasons stated above, I will issue the attached Approvable letter with draft labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 20-982
HFD-120
HFD-120/Katz/Laughren/Dubitsky/Shin

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 2, 1999

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Paxil CR (paroxetine controlled release tablets) for the treatment of panic disorder

TO: File NDA 20-982
[**Note:** This overview should be filed with the 4-22-98 original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression in an immediate release formulation, i.e., Paxil (NDA 20-031, approved December, 1992) and also in the delayed and extended release formulation, i.e., Paxil CR (NDA 20-936, approved 2-16-99), proposed for panic disorder in this application. The immediate release formulation of paroxetine is also approved for OCD and panic disorder. Paxil CR is recommended for qd dosing, as is the immediate release formulation, Paxil. The recommended initial dose for Paxil CR in panic disorder is 12.5 mg/day, with increases up to a maximum dose of 75 mg/day as needed.

At the present time, there are only 4 drugs approved for the treatment of panic disorder in the US, i.e., alprazolam, clonazepam, Zoloft, and as noted, Paxil immediate release tablets.

SKB requested a meeting with the Division even prior to submission of an IND for the controlled release formulation, in order to seek feedback on their planned development program. Although they have not made comparative claims of superior safety in the NDAs subsequently submitted, it was clear at the 7-3-96 meeting that a major rationale for the new formulation was to develop a product less likely to induce nausea, by virtue of its delayed and then more gradual absorption, compared to the immediate release paroxetine. We emphasized the need for carefully conducted studies that would compare the CR and IR forms at equieffective points on the dose response curves for the two formulations. We also suggested that, rather than planning multiple studies for depression, they plan single studies for each of their currently approved indications, i.e., depression, OCD, and panic disorder. They did not accept our advice on either matter, and have not done studies that adequately

address the issue of comparative safety of the two formulations. Presumably they are satisfied with a simple claim of safety and effectiveness for depression and other indications for the CR formulation compared to placebo.

The sponsor submitted protocols for 3 panic disorder studies (494, 495, and 497) on 10-17-96 under

No preNDA meeting was held for this application.

Since the proposal is to use the currently approved Paxil CR controlled release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Greg Dubitsky, M.D., from the clinical group. Kallappa Koti, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original application for this expanded indication was submitted 4-22-98, and the application was considered adequate for filing on 6-16-98.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Paxil CR tablets are already approved, there are no CMC issues requiring review for this application.

3.0 PHARMACOLOGY

As Paxil CR tablets are already approved, there are no pharmacology/toxicology issues requiring review for this application.

4.0 BIOPHARMACEUTICS

Paxil CR is intended for qd dosing. Paxil CR both delays dissolution with an enteric coat (about 4 hour absorption lag time) and slows the rate of absorption by the use of a polymeric matrix for dispersion (about 25% reduction in rate of absorption). Paxil CR is about 25% less available than Paxil IR; this difference is the basis for the 25% greater dosing of Paxil CR vs Paxil IR in the phase 2-3 clinical trials. The single and multiple-dose pharmacokinetics of Paxil CR have been characterized. There was a 31% reduction in peak to trough plasma level fluctuation for Paxil CR compared to Paxil IR. Although in single dose food studies there was a further delay in absorption with food, Cmax and AUC were unaffected in the steady state food study.

As Paxil CR tablets are already approved, there are no biopharmaceutics issues requiring review for this application.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 randomized, multicenter, placebo-controlled, double-blind, parallel group, flexible-dose, 10-week trials in adult outpatients with a diagnosis of panic disorder with or without agoraphobia (DSM-IV). Patients could not have had another Axis I condition considered as the primary diagnosis within the preceding 6 months. In all studies, assignment was to Paxil CR or placebo (1:1), with treatment initiated at 12.5 mg/day for the first week, followed by dose increases at weekly increments of 12.5 mg, as needed for symptom control, to a maximum dose of 75 mg/day. Patients recorded information on panic attacks in daily diaries, and the protocol specified primary outcome for all three studies was the percentage of patients in each treatment group meeting a response criterion of zero full panic attacks at study endpoint. Secondary outcomes included (1) number of full panic attacks, (2) CGI severity, (3) percentage of time spent with anticipatory anxiety, and (4) the Marks-Sheehan Phobia Scale fear and avoidance scores. Logistic regression was used in the analyses of the primary outcome of percent responders based on zero full panic attacks. Change from baseline in CGI Severity scores was analyzed using the Wilcoxon rank sum test, and the other secondary outcomes were analyzed using analysis of variance. It should be noted that there was no prior agreement with the sponsor on what outcomes would be critical to deciding whether or not the results from a particular trial could be considered positive. Thus, I have focused on the outcomes that we have generally considered key in evaluating data for panic disorder studies, i.e., change from baseline in full panic attacks, percentage of patients achieving zero full panic attacks, and change from baseline in CGI severity scores.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 494

This was a US study involving 33 sites. There were approximately 140 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 74% & 76%, respectively. Patients had a mean age of roughly 38, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 48 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-4 for Paxil CR vs -3 for placebo), but this difference did not achieve statistical significance (p=0.08). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior but with a p-value that again missed statistical significance (p=0.07).

In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (69% for Paxil CR vs 50% for placebo, yielding an odds ratio of 2.2), and this difference was statistically significanc (p=0.003). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior with a statistically significant p-value (p=0.005). In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was statistically significantly superior to placebo (p=0.03). In the OC analysis at weeks 9-10, Paxil CR was again statistically significantly superior to placebo (p=0.007).

While the results are not entirely consistent, in my view, they are sufficient to consider this a positive study. Thus, I agree with Dr. Dubitsky's conclusion that this study is positive. Dr. Koti also considered this a positive study, based mostly on the results for the proportion of patients free of panic attacks at endpoint.

5.1.2.2 Study 495

This was a US study involving 29 sites. There were approximately 160 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 67% & 76%, respectively. Patients had a mean age of roughly 37, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 48 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-5 for Paxil CR vs -3 for placebo), and this difference did achieve statistical significance (p<0.001). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior with a p-value that achieved statistical significance (p=<0.001).

In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (57% for Paxil CR vs 50% for placebo, yielding an odds ratio of 1.3); however, this difference was not statistically significant (p=0.26). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior (71% for Paxil CR vs 55% for placebo, yielding an odds ratio of 2.0), with a statistically significant p-value (p=0.03).

In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was statistically significantly superior to placebo (p=0.004). In the OC analysis at weeks 9-10, Paxil CR was again statistically significantly superior to placebo (p=<0.001).

These results are are again sufficient, in my view, to consider this a positive study. Thus, I agree with Dr. Dubitsky's conclusion that this study is positive. Dr. Koti considered this study supportive since the results were statistically significant on the proportion of patients free of full panic attacks only in the OC analysis, and not in the LOCF analysis. However, the results on the other 2 variables I consider critical in interpreting this study were highly significant on both OC and LOCF analyses, and thus overcame, in my view, the inconsistency on the third outcome of interest.

5.1.2.3 Study 497

This was a US study involving 29 sites. There were approximately 140 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 70% for both groups. Patients had a mean age of roughly 39, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 51 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-4 for Paxil CR vs -3 for placebo), but this difference did not achieve statistical significance (p=0.24). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior but with a p-value that did not achieve statistical significance (p=0.08).
In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (63% for Paxil CR vs 56% for placebo, yielding an odds ratio of 1.4); however, this difference was not statistically significant (p=0.23). In the OC analysis at weeks 9-10, Paxil CR was again numerically but not statistically significantly superior to placebo (p=0.53).

In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was not statistically significantly superior to placebo (p=0.08). In the OC analysis at weeks 9-10, Paxil CR was again not statistically significantly superior to placebo (p=0.12).

These results are are not sufficient, in my view, to consider this a positive study. Thus, I agree with Dr. Dubitsky's and Dr. Koti's conclusions that this study is negative. There was no active control arm to test the sensitivity of the study to detect a treatment effect.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil CR in the Treatment of Panic Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this development program pertinent to the issue of dose/response for the CR formulation, and there were also insufficient data pertinent to this issue in the original NDA for panic disorder for the immediate release product. Thus, one can at most recommend dosing patients in the ranges utilized and on the incremental schedule utilized in the trials supporting the effectiveness of this new formulation.

Clinical Predictors of Response

While there was a very limited potential for detecting subgroup interactions on the basis of demographics, severity of illness, or other covariates, there was no pattern of findings suggestive of any such interactions.

Size of Treatment Effect

One of the difficulties in assessing treatment effect size in panic disorder studies is that there is often a large placebo response. That was certainly the case here, even more so than for the Paxil immediate release program. Consequently, the drug placebo difference is not as quite as impressive for these data compared to those for the immediate release program, especially when looking at % responders based on zero full panic attacks, as Dr. Dubitsky has done. However, when looking at difference in change from baseline in the mean number of full panic attacks, the result is roughly the same for both programs, i.e., a difference between drug and placebo of roughly 1-2 panic attacks. This treatment effect is also comparable to what we have seen for the other drugs approved for the treatment of panic disorder.

Duration of Treatment

While there were no data in this development pertinent to duration of effect, there were data suggestive of longer-term effectiveness for panic disorder for the immediate release product, and it would not be unreasonable, in my view, to extrapolate from those data to the CR formulation.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence from two trials to support the claim of effectiveness for Paxil CR in the treatment of panic disorder. While the third study was negative, I consider the data in the aggregrate sufficient to extend the anti-panic claim to this controlled release formulation of paroxetine.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for paroxetine CR were reviewed by Dr. Dubitsky. This original review was based on an integrated database with a cutoff date of 10-22-97 for the 1 phase 1 study (569: an open label PK study) and the 3 phase 2-3 studies (494, 495, 497; described under Efficacy Data) for this development program. The total paroxetine CR exposed sample consisted of n=80 normal volunteers in the single dose PK study and n=444 panic disorder patients in the 3 clinical studies. The demographics and dosing for the patients were previously summarized under Efficacy Data. Dr. Dubitsky has also very recently reviewed the paroxetine CR safety data for the Paxil CR depression program, consisting of n=371 normal volunteers and n=316 depressed patients.

Adverse Event Profile for Paroxetine CR

Given our extensive knowledge of the safety profile for immediate release paroxetine, and our recent review of paroxetine CR exposures in the Paxil CR depression program in a similar dose range to that proposed for the treatment of panic disorder, the focus in the safety review was on any differences

between the recognized safety profile for this drug, both in the immediate and controlled release formulations, in its approved indications from that observed in the panic disorder population.

Overall, the side effect profile of paroxetine CR in the panic disorder population was as expected for this SSRI and not obviously different from that of the immediate release product in the various populations in which it has been studied, including panic disorder, or from this same controlled release product in a depressed population. There were no new, unrecognized serious adverse events that could be considered related to paroxetine CR use or that would impact on the labeling of this product.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

There were no published papers specifically concerning the CR formulation of paroxetine. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Paxil CR is not marketed anywhere at this time. We will ask for an update on the regulatory status of Paxil CR for panic disorder in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Paxil CR for panic disorder to the PDAC.

9.0 DSI INSPECTIONS

Although DSI did not conduct investigations specific to this application, they did check the list of investigators for those previously inspected and classified as VAI-3 or worse. Only 1 investigator, Dr. Cal Cohn, was in that category. He is on the "restricted" list, but the requirement for third party verification has apparently been met. Consequently, there was no need to exclude data from this investigator.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have modified the sponsor's draft dated 4-22-98.

10.2 Foreign Labeling

Paxil CR is not marketed anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil CR is effective and acceptably safe in the treatment of panic disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 20-982 (Paxil CR/Panic Disorder)
HFD-120/Div File
HFD-120/TLaughren/RKatz/GDubitsky/MShin

DOC: MEMPXRPD.AE1

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA #_20982__
Drug _Paxil CR (paroxetine HCL) controlled-release 12.5 & 25mg Tablets DATE_ 04/22/98____
Applicant_SmithKline Beecham___CSO_Melaine Shin__/Phone_x 4-5527_____
User Fee Goal Date:_04/22/99_____

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures	AP_____AE__X__ NA_____
Are there any Phase 4 commitments?	Yes_____ No___X_____
2. Have all disciplines completed their reviews?	Yes___X____ No_____
If no, what review(s) is/are still pending?	_____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types__3S___
4. LABELING (package insert and carton and container labels).	Draft_____
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Revised Draft_____X_____ Final_____
5. PATENT INFORMATION	____X_____
6. EXCLUSIVITY CHECKLIST	____X_____
7. PEDIATRIC PAGE	____X_____
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	__X____
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES	__Memo___
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	_____X_____
GROUP LEADER'S MEMO	_____X_____
MEDICAL REVIEW	_____X_____
SAFETY UPDATE REVIEW	_____N/A_____
STATISTICAL REVIEW	_____X_____
BIOPHARMACEUTICS REVIEW	_____X_____
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	_____Memo_____
Statistical Review of Carcinogenicity Study(ies)	_____N/A_____
CAC Report/Minutes	_____N/A_____
CHEMISTRY REVIEW	_____X_____
Labeling and Nomenclature Committee Review Memorandum	_____X_____
Date EER completed __8/4/98___ (attach signed form or CIRTS printout) FUR needed __n/a___ FUR requested _n/a___	OK__X___ No_____
Have the methods been validated?	Yes (attach)_____ No__X___
Environmental Assessment Review / FONSI	Review __n/a____ FONSI_n/a___
MICROBIOLOGY REVIEW	_____n/a_____
What is the status of the monograph?	_____
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	_____X_____
12. MINUTES OF MEETINGS	_____X_____
Date of End-of-Phase 2 Meeting	___n/a_____
Date of pre-NDA Meeting	___n/a_____
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes_____ Info Alert_____ Transcript_____ No mtg__X___
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	_____n/a_____
15. If approval letter, has ADVERTISING MATERIAL been reviewed?	Yes_____ No__n/a_____
If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes, documentation attached_____ No, included in AP ltr _____
16. INTEGRATED SUMMARY OF EFFECTIVENESS	_____X_____
17. INTEGRATED SUMMARY OF SAFETY	_____X_____

revision: 3/7/96

Paxil® CR (paroxetine hydrochloride)
Controlled-Release Tablets

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R.314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006 The patent expiration date shown above was calculated in accordance with the U.S. Patent and Trademark Office's Federal Register notice of March 27, 1995. SB believes, however, that the correct expiration date, as properly calculated in accordance with the law and in particular with Section 532 of the Uruguay Round Agreements Act, P.L. 103-564, is September 24, 2008. SB reserves the right to modify the patent data in the future. SB also reserves the right to assert this position against persons or parties who may seek to make, use, offer for sale, import, or sell the approved drug prior to September 24, 2008.	Drug	Beecham Group p.I.c. Brentford, England

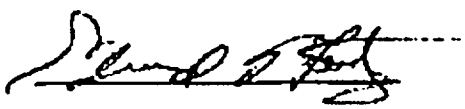
(continued on next page)

Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

4 839 177	June 13, 2006	Drug Product	Jagotec AG, Hergiswill, Switzerland	Parkhurst, Oliff & Berridge
5 422 123	June 6, 2012	Drug Product	Jagotec AG, Hergiswill, Switzerland	Birch, Stewart, Kolasch & Birch

The undersigned declares that Patent No's 4 839 177 and 5 422 123 cover the formulation, composition and/or method of use of paroxetine hydrochloride controlled release formulation. This product is the subject of this application for which approval is being sought:

SmithKline Beecham

By: 

Edward T. Lentz
Vice President & Director
Corporate Intellectual Property - US

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-982 SUPPL #_____

Trade Name Paxil CR Generic Name: Paroxetine HCL Controlled Release 12.5&25mg Tablets

Applicant Name: SmithKline Beecham HFD - 120
Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-031 Paxil (paroxetine HCL) Immediate Release 10, 20, 30, and 40mg Tablets

NDA# 20-936 Paxil CR (paroxetine HCL) Controlled Release 12.5 and 25mg Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 494

Investigation #2, Study # 495

Investigation #3, Study # 497

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES/___/	NO/_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1,	Study # 494
Investigation #2,	Study # 495
Investigation #3,	Study # 497

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

_____ YES /_X_/ NO /___/ Explain: _____

Investigation #2

_____ YES /_X_/ NO /___/ Explain: _____

Investigation #3

_____ YES /_X_/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

APPEARS THIS WAY
ON ORIGINAL

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

/S/ 3/9/99

Signature of preparer Date

Title: CSO/PM

/S/ 3/9/99

Signature of ~~Office~~/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

Ln 3/9/99

NDA/BLA Number:	20982	**Trade Name:**	PAXIL CR (PAROXETINE HCL) TABS 12.5MG
Supplement Number:		**Generic Name:**	PAROXETINE HCL TABS 12.5MG
Supplement Type:		**Dosage Form:**	CRT
Regulatory Action:	AE	**Proposed Indication:**	Panic Disorder, with or without agoraphobia

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission? N/A

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
3/5/99 Since the diagnosis of panic disorder generally would not be made in pediatric patients, there is no need for pediatric information in labeling re: this diagnosis and no need for a phase 4 commitment to conduct studies in pediatric patients with this disorder.

Studies are ongoing (studies being conducted on the immediate release formulation, NDA 20-031)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LANA CHEN

/S/

Signature

3/5/99

Date

DEBARRMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham hereby certifies that, to the best of its knowledge and belief, we did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20982/000**
Stamp: **22-APR-1998** Regulatory Due: **22-APR-1999**
Applicant: **SKB PHARMS**
1250 SOUTH COLLEGEVILLE RD
COLLEGEVILLE, PA 194260989

Priority: **3S** Org Code: **120**
Action Goal: District Goal: **21-DEC-1998**
Brand Name: **PAXIL CR (PAROXETINE HCL) TABS 12.5/25MG**
Established Name:
Generic Name: **PAROXETINE HCL TABS 12.5/25MG**
Dosage Form: **CRT (CONTROLLED RELEASE TABL**
Strength: **12.5,25,37.5,50 MG**

FDA Contacts:
A. HOMONNAY WEIKEL (HFD-120) 301-594-5535 , Project Manager
R. LOSTRITTO (HFD-570) 301-594-5564 , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation:

ACCEPTABLE on 04-AUG-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9612240**
SMITHKLINE BEECHAM
MANOR RD WEST RH10 2QJ
CRAWLEY, ENGLAND - WEST SUSS
DMF No:
AADA No:

Profile: **TCT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **04-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: **9610449**
SMITHKLINE BEECHAM CHEMICA
AYRSHIRE, SCOTLAND
, IRVINE, UK
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **07-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE RELEASE TESTER

APPEARS THIS WAY
ON ORIGINAL

Consult #841 (HFD-120)

PAXIL CR paroxetine hydrochloride controlled release tablets

There were no look-alike/sound-alike conflicts noted or misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 9/9/97, Chair
CDER Labeling and Nomenclature Committee

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 22, 1999
FROM: Alfreda Burnett, HFD-344
TO: Melaine Shin, HFD-120
SUBJECT: NDA 20-982: Paxil CR (paroxetine HCl)
Panic Disorder

On April 22, 1998 SmithKline Beecham submitted NDA 20-982 for Paxil CR for the treatment of Panic Disorder. Paxil is already an approved drug product, this NDA covers a new formulation and new indication. DSI does not routinely assign inspections of new formulations or new indications. We have reviewed the list of investigators for those previously inspected and classified as VAI-3 or worse.

C [redacted] A requirement of this restriction is that there be third party verification of subject identification. The sponsor has submitted verification of subject identification. The data from his site can be used to support the approval requests for this NDA.

/s/ Alfreda Burnett

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Nov-1998 11:20am EST
From: Anna Marie Homonnay
HOMONNAYA
Dept: HFD-120 WOC2 4025
Tel No: 301-594-5535 FAX 301-594-3839

O: Alfreda Burnett (BURNETTA)

ubject: FWD: re: NDA 20-982/Paxil CR/Panic

lfreda,

nstead of calling, I think it's better if I forward you our request with egards to DSI. Please let me know if you have anymore questions.

nna Marie

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Nov-1998 09:30am EST
From: Anna Marie Homonnay
HOMONNAYA
Dept: HFD-120 WOC2 4025
Tel No: 301-594-5535 FAX 301-594-3839

O: Greg Dubitsky (DUBITSKYG)

C: Thomas Laughren (LAUGHREN)

ubject: re: NDA 20-982/Paxil CR/Panic

reg,

SI called today to check which of the clinical trials would be considered
ore pivotal than the other since they are planning to choose to inspect one?

hanks,

nna Marie

Request for Audit

DATE: October 27, 1998

FROM: Division of Neuropharmacological Drug Products, HFD-120.

SUBJECT: Request for Study-Oriented Audits for sNDA

TO: DSI Staff: Alfreda Burnett

Please refer to a correspondence to Dr. Robert Young dated May 27, 1998, from SmithKline Beecham Pharmaceuticals regarding NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

Please audit any sites as necessary. The due date of this application is 4/22/99. If you should have any questions, please contact: Ms. Anna M. Homonnay-Weikel, Project Manager at (301) 594-5535.

SB
SmithKline Beecham
Pharmaceuticals

DUPLICATE

May 27, 1998

Anna M. Homonnay-Weikel
Project Manager

Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

CENTER FOR DRUG EVALUATION AND RESEARCH

MAY 28 1998

RECEIVED HFD-120

Agency Request for Information

ORIG AMENDMENT
NCBM

Dear Anna,

Reference is made to NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

Submitted herein, in duplicate, is a list of investigators pertaining to the aforementioned application. As we discussed on the phone, a duplicate copy of this submission also has been sent to:

Dr. Robert Young
Food and Drug Administration
7520 Standish Place
Route 125
Rockville, Maryland 20855

Please do not hesitate to contact me at (610) 917-5970 should you have any questions or need any additional information.

Sincerely,

Thomas F. Kline
Manager
US Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917-7000 Fax (610) 917-7707

Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

for Panic Disorder

NDA 20-982

List of Investigators (and No. of Patients): Alphanumeric by Protocol

For clinical studies 29060/494, 495 and 497

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 494					
Apter, Jeffrey T., M.D. Princeton Biomedical Research 256 Bunn Drive Suite 6 Princeton, NJ 08540 *and* Princeton Biomedical Research Axelrad Building 809 River Rd (Rt 9) Lakewood, NJ 08701	United States	494/001	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Bielski, Robert J., M.D. Institute for Health Studies 26105 Orchard Lake Rd. Suite 301 Farmington Hills, MI 48334 *and* Institute for Health Studies 825 Parchment Dr., S.E. Grand Rapids, MI 49546 *and* Institute for Health Studies 4084 Okemos Road Suite C Okemos, MI 48864	United States	494/002	4	5	9
Bremner, James D., M.D. Bremner Research Institute, Inc. 1021 West 4th - Suite G Olympia, Washington 98502	United States	494/003	2	2	4
Bystritsky, Alexander, M.D. University of California, Los Angeles 300 UCLA Medical Plaza, Suite 2200 Los Angeles, CA 90095	United States	494/004	4	5	9
Carman, John S., M.D. Carman Research 4015 South Cobb Drive Suite 245 Smyrna, GA 30080	United States	494/005	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Dave, Mahesh R., M.D. Sciman Biomedical Research, Inc. 1303 Memorial Drive Bryan ,Texas 77802 *and* Sciman Biomedical Research, Inc. 2901 E. 29th Street, Suite 117 Bryan, Texas 77802	United States	494/006	4	4	8
Feiger, Alan, P.C., M.D. Feiger Health Research Center 3003 E. Third Avenue Denver, CO 80206 *and* Feiger Health Research Center 3555 Lutheran Pkwy, Suite 320 Wheat Ridge, CO 80033	United States	494/007	4	5	9
Helfing, Saul H., M.D. Hill top Research 5331 SW Macadam Avenue, Suite 210 Portland, OR 97201	United States	494/008	12	12	24
Hollander, Eric, M.D. Department of Psychiatry, Box 1230 Mount Sinai School of Medicine One Gustave L. Levy Place New York, NY 10029	United States	494/009	2	2	4

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Houck, Carl A., M.D. University of Alabama at Birmingham Department of Psychiatry/Clinical Research Professional Arts Building, Suite 302 1025 18th Street South Birmingham, AL 35205	United States	494/010	1	0	1
Jefferson, James W., M.D. Dean Foundation for Health, Research and Education 8000 Excelsior Drive, Suite 302 Madison, WI 53717-1914	United States	494/011	2	4	6
Kennedy, Barbara L., M.D., Ph.D. Department of Psychiatry and Behavioral Sciences School of Medicine University of Louisville Louisville, KY 40202	United States	494/012	3	4	7
Londborg, Peter D., M.D. Seattle Clinical Research Center, Inc. Cabrini Medical Tower 901 Boren Ave., Suite 1800 Seattle, WA 98104	United States	494/013	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Miller, Kevin, M.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Joan Busner, Ph.D. and Jeff Gall, M.D.* Busner, Joan, Ph.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Kevin Miller, M.D.* Gall, Jeff, M.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Kevin Miller, M.D.)*	United States	494/014	3	4	7
Pavlinac, Dennis M., M.D. 3907 Waring Road, Suite 3 Oceanside, CA 92056	United States	494/015	3	3	6
Rea, William S., M.D. Clinical Studies, Fort Lauderdale 108 N.E. 1st Street Fort Lauderdale, FL 33301	United States	494/016	6	7	13

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Reiman, Eric M., M.D. Good Samaritan Regional Medical Center Samaritan Behavioral Health 925 E. McDowell Road - 4th Floor Phoenix, AZ 85006	United States	494/017	5	4	9
Schweizer, Edward, M.D. Mood & Anxiety Disorders Section University Science Center 3600 Market Street Philadelphia, PA 19104-2649	United States	494/018	0	0	0
Sheehan, David V., M.D. University of South Florida College of Medicine, Dept. of Psychiatry 3515 E. Fletcher Ave. Tampa, FL 33613-4788	United States	494/019	10	10	20
Shelton, Richard C., M.D. Vanderbilt University Medical Center 2200 Village at Vanderbilt 1500 21st Ave, South Nashville, TN 37212	United States	494/020	5	6	11
Smith, Ward T., M.D. Pacific Northwest Clinical Research Center 9495 S.W. Locust, Suite E Portland, OR 97223 *and* Pacific Northwest Clinical Research Center 2212 Lloyd Center Portland, OR 97232	United States	494/021	5	5	10

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Stein, Murray B., M.D. UCSD Department of Psychiatry Anxiety & Traumatic Stress Disorders Program 8950 Villa La Jolla Dr., Ste #2243 La Jolla, CA 92037	United States	494/022	3	4	7
Targum, Steven D., M.D. Philadelphia Medical Institute 1015 Chestnut St., Suite 1303 Philadelphia, PA 19107 *and* Crozer-Chester Medical Center Old Main President's Blvd. Upland, PA 19013	United States	494/023	2	4	6
Thompson, Peter M., M.D. University of New Mexico Health Sciences Center Department of Psychiatry, Research Office/Lab 943 Stanford Drive NE. Medical Bldg. 6 Albuquerque, NM 87131-5326	United States	494/024	6	6	12
Trivedi, Madhukar H., M.D. University of Southwestern Medical Center St. Paul POB I, Suite #520 5959 Harry Hines Blvd. Dallas, TX 75235-9101	United States	494/025	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Weihs, Karen, M.D. Clinical Psychiatric Research Center George Washington University Medical Center Ross Hall R,. 730 2300 eye Street, N.W. Washington, DC 20037	United States	494/026	8	7	15
Merideth, Charles H., M.D. Affiliated Research Institute 8880 Rio San Diego Drive, Suite 1090 San Diego. CA 92108	United States	494/027	7	7	14
Donley, Patrick J., M.D. Puget Sound Medical Research A Division of Hill Top Research, Ltd. 6210 75th St. West, Suite A200 Tacoma, WA 98467	United States	494/028	4	4	8
Simon, Jeffrey S., M.D. Northbrooke Research Center 4600 West Schroeder Drive Brown Deer, WI 53223	United States	494/029	2	1	3
Kaplan, Barnett, M.D. Rainer Clinical Research Center 4033 Talbot Road South, #500 Renton, WA 98055 *and* Southlake Professional Group 1400 Talbot Road South, #203 Renton, WA 98055	United States	494/030	1	1	2

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Hartford, Madelon, M.D. Hartford Research Group 3120 Burnet Avenue Suite 103 Cincinnati, OH 45229	United States	494/031	3	3	6
Mattes, Jeffrey A., M.D. Psychopharmacology Research Association of Princeton Princeton Professional Park 601 Ewing St., Ste A-12 Princeton, NJ 08540	United States	494/032	4	4	8
Davis, Larry M., M.D. Broad Ripple MedCheck 1091 Broad Ripple Avenue Indianapolis, IN 46220 *and* Davis Clinic, P.C. 1431 North Delaware Street Indianapolis, IN 46202	United States	494/033	4	3	7

APPEARS THIS WAY
ON ORIGINAL

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 495					
Adler, Lawrence W., M.D. Clinical Insights, Inc. 1600 Crain highway South, Suite 601 Glen Burnie, MD 21061 *(Co-Investigator with Marc Hertzman, M.D.)* *and* Clinical Research Center 1600 Crain Highway South, Suite 410 Glen Burnie, MD 21061 *(Co-Investigator with Marc Hertzman, M.D.)* Hertzman, Marc, M.D. Clinical Research Center 1600 Crain Highway South, Suite 410 Glen Burnie, MD 21061 *(Co-Investigator with Lawrence W. Adler, M.D.)* *and* Clinical Insights, Inc. 1600 Crain highway South, Suite 601 Glen Burnie, MD 21061	United States	495/001	6	7	13

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Beitman, Bernard D., M.D. University of Missouri-Columbia University School of Medicine One Hospital Drive Columbia, MO 65212 *(Co-Investigator with Lee Ann Kelley, M.D.)* Kelley, Lee Ann M.D. University of Missouri-Columbia University School of Medicine One Hospital Drive Columbia, MO 65212 *(Co-Investigator with Bernard D Beitman, M.D.)*	United States	495/002	3	3	6
Bell, Jon, M.D. University of Colorado Health Sciences Center Anxiety and Mood Disorders Clinic C-261-72 4200 E. 9th Avenue Denver, CO 80262	United States	495/003	4	4	8
Burke, William, M.D. Psychopharmacology Research Center University of Nebraska Medical Center 600 South 42nd Street Omaha, NE 68198-5575	United States	495/004	2	4	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Davis, Larry M., M.D. Davis Clinic, P.C. 1431 North Delaware Street Indianapolis, IN 46202 *and* Broad Ripple MedCheck 1091 Broad Ripple Ave. Indianapolis, IN 46220	United States	495/005	16	16	32
DuPont, Robert, M.D. Institute for Behavior and Health 6191 Executive Blvd. Rockville, MD 20852	United States	495/006	2	1	3
England, Donald L., M.D. PeaceHealth Medical Group 1162 Williamette Street Eugene, OR 97401	United States	495/007	8	8	16
Depriest, Michael, M.D. Pharmacology Research Corporation 516 south 6th Street, Suite 100 Las Vegas, NV 89104 *(Co-Investigator with James M. Ferguson, M.D.)* Ferguson, James M., M.D. Pharmacology Research Corporation 516 south 6th Street, Suite 100 Las Vegas, NV 89104 *(Co-Investigator with Michael Depriest, M.D.)*	United States	495/008	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Gorman, Jack, M.D. Phobia Clinic, Hillside Hospital Long Island Jewish Medical Center 75-59 263rd Street Glen Oaks, NY 11004 *(Co-Investigator with Laszlo Papp, M.D.)* Papp, Laszlo, M.D. Phobia Clinic, Hillside Hospital Long Island Jewish Medical Center 75-59 263rd Street Glen Oaks, NY 11004 *(Co-Investigator with Jack Gorman, M.D.)*	United States	495/009	5	5	10
Hartford, James T., M.D. Hartford Research Group 273 Regency Ridge Dayton, OH 45459	United States	495/010	12	12	24
Heiser, Jon F., M.D. Pharmacology Research Institute 1000 Dove Street, Suite 200 Newport Beach, CA 92660-2814 *and* 3505 Long Beach Blvd., Suite 2F Long Beach, CA 90807-3947	United States	495/011	2	1	3

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Kalali, Amir, M.D. The Irvine Clinical Research Center 16259 Laguna Canyon Road Irvine, CA 92618 *(Co-Investigator with Sid Rosenblatt, M.D.)* Rosenblatt, Sid, M.D. The Irvine Clinical Research Center 16259 Laguna Canyon Road Irvine, CA 92618 *(Co-Investigator with Amir Kalali, M.D.)*	United States	495/012	8	8	16
Mattes, Jeffrey A., M.D. Psychopharmacology Research Association of Princeton Princeton Professional Park 601 Ewing Street, Suite A-12 Princeton, NJ 08540	United States	495/013	12	13	25
Nemeroff, Charles B., M.D., Ph.D. Emory University Department of Psychiatry & Behavioral Sciences 1701 Uppergate Drive, Room 126 Atlanta, GA 30322 *(Co-Investigator with Philip T. Ninan, M.D.)* Ninan, Philip T, M.D. Emory University Department of Psychiatry & Behavioral Sciences 1701 Uppergate Drive, Room 126 Atlanta, GA 30322 *(Co-Investigator with Charles B. Nemeroff, M.D., Ph.D.)*	United States	495/014	1	2	3

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Patterson, William M., M.D. Birmingham Research Group, Inc. 2120 Lynngate Drive Birmingham, AL 35216	United States	495/016	5	6	11
Pollack, Mark H., M.D. Massachusetts General Hospital ACC-815, 15 Parkman Street Boston, MA 02114	United States	495/017	3	4	7
Resnick, Harvey, M.D. 321 E. Phillips Road Angleton, TX 77515 *and* 135 Oyster Creek Drive Suites S & W Lake Jackson, TX 77566 *and* 201 Oak Drive South Suites 102, 107 & 204 Lake Jackson, TX 77566 *and* 52 Flag Lake Plaza Lake Jackson, TX 77566 *and* 106 Circle Way Lake Jackson, TX 77566	United States	495/018	5	4	9
Rosenthal, Murray H., D.O. 9449 Balboa Avenue Suite 205 San Diego, CA 92123	United States	495/019	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Strawn, Steven K., M.D. Freedom Research, Inc. 1303 FM 2818 East College Station, TX 77840	United States	495/020	2	1	3
Telew, Nicholas W., M.D. OCCI 132 East Broadway Suite 332 Eugene, Oregon 97401 *and* Mental Health Match 175 West B Street Building B Springfield, Oregon 97401 *and* Oakway Internal Medicine 495 Oakway Road Eugene, Oregon 97401	United States	495/021	14	13	27
Templeton, Richard K., M.D. The Psychiatric Research Group 110 Annapolis Street Annapolis, MD 21401	United States	495/022	4	5	9
Tucker, Phebe, M.D. University of Oklahoma Health Science Center Department of Psychiatry 920 Stanton L. Young Blvd. (5SP520) Oklahoma City, OK 73104	United States	495/023	5	5	10

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Weisler, Richard H., M.D. Duke University Medical Centre Ervin Drive Durham, North Carolina 27709 *and* 900 Ridgefield Drive, Suite 320 Raleigh, North Carolina 27609	United States	495/024	9	6	15
Weiss, Kenneth J., M.D. 722 E. Butler Pike Ambler, PA 19002 *and* 400 Market Street P.O. Box 1990 Camden, NJ 08101 *and* 2792 Egypt Road Audubon, PA 19403 *and* Suburban Psychiatric Assoc. 600 N. Jackson Street Media, PA 19063 *and* Delaware Valley Research Assoc. 133 Ivy Lane King of Prussia, PA 10406	United States	495/025	9	9	18
Charles, Lorna, M.D. Southern New Jersey Medical Institute 9 East Laurel Road Stratford, NJ 08084	United States	495/026	4	3	7

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Cunningham, Lynn A., M.D. Vine Street Clinic 301 No. Sixth St., Suite 330 Springfield, IL 62701 *and* Clinical Research Associates of Edwardsville 1121 University Drive Edwardsville, IL 62025	United States	495/027	1	2	3
Stack, Jack M., M.D. Gratiot Community Hospital 300 Warwick Alma, MI 48801	United States	495/028	2	2	4
Goldstein, Susanna, M.D. Center for Psychobiology 65 Central Park West, # 1BR New York, NY 10023	United States	495/030	5	6	11
Stoltz, Randall R., M.D. GFI Pharmaceutical Services, Inc. 800 St. Mary's Drive Evansville, IN 47714	United States	495/031	3	4	7

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 497					
Bastini, Bijan, M.D. North East Ohio Health Services One Commerce Park Square 23200 Chagrin Blvd., Suite 400 Beachwood, OH 44122 *and* Portage Path CMHC 340 South Broadway St. Akron, OH 44308	United States	497/001	1	1	2
Brown, David, M.D. Community Clinical Research, Inc. 4411 Medical Parkway Austin, Texas 78756	United States	497/002	8	7	15
Bryer, Joseph, M.D. Clary Research Associates, P.A. 575 South duPont Highway New Castle, DE 19720	United States	497/003	3	3	6
Cohn, Cal K., M.D. The Cohn Center 7777 Southwest Freeway Suite 1036 Houston. TX 77074	United States	497/004	16	16	32

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Delgado, Pedro, M.D. University of Arizona Health Science Center 1501 N. Campbell Ave. Tucson, AZ 85724 *(Co-Investigator with Alan Gelenberg, M.D.)* Gelenberg, Alan, M.D. University of Arizona Health Science Center 1501 N. Campbell Ave. Tucson, AZ 85724 *(Co-Investigator with Delgado, Pedro, M.D.)*	United States	497/005	6	7	13
DuBoff, Eugene A., M.D. Center for Behavioral Medicine 4704 Harlan Street Suite 430 Denver, CO 80212	United States	497/006	6	4	10
Ferguson, James M., M.D. Pharmacology Research Corporation Commerce Park 448 East 6400 South, Suite 350 Salt Lake City, Utah 84107	United States	497/007	7	7	14
Haefner, Gregory, M.D. Wein Center (1st Floor MRI Building) Mount Sinai Medical Center 4300 Alton Road Miami Beach, FL 33140	United States	497/008	5	6	11
Holland, Peter J., M.D. 7280 W. Palmetto Park Road #203 Boca Raton, FL 33433	United States	497/009	5	4	9

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Kavoussi, Richard J., M.D. Allegheny University of the Health Sciences EPPPI Room 250A 3200 Henry Avenue Philadelphia, PA 19129	United States	497/010	2	2	4
Khan, Arifulla, M.D. Hambleton Professional Building 10126 NE 132nd Suite B Kirkland, WA 98034	United States	497/011	8	7	15
Landbloom, Ronald, M.D. St. Paul-Ramsey Medical Center 640 Jackson Street St. Paul, MN 55101	United States	497/012	4	3	7
Leefeldt, Randall Henshaw, M.D. Sutter Institute for Medical Research 2801 K Street, Suite 505 Sacramento, CA 95816 *and* Sutter Community Clinic - Fruitridge 1740 Fruitridge Road Sacramento, CA 95822	United States	497/013	2	2	4
Lydiard, R. Bruce, M.D., Ph.D. Medical University of South Carolina 171 Ashley Avenue Charleston, South Carolina 29425	United States	497/014	7	7	14

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Murphy, John J., M.D. 820 W. Service Avenue West Corina, CA 91790 *(Co-Investigator with Dennis J. Munjack, M.D.)* Munjack, Dennis J., M.D. 820 W. Service Avenue West Corina, CA 91790 *(Co-Investigator with Murphy, John J., M.D.)*	United States	497/015	6	6	12
Reimherr, Fred W., M.D. Department of Psychiatry University of Utah Health Sciences Center Mood Disorders Clinic 50 North Medical Drive Salt Lake City, UT 84132	United States	497/016	3	4	7
Riesenberg, Robert A., M.D. BioBehavioral Associates 625 DeKalb Industrial Way Decatur, GA 30033	United States	497/017	12	9	21
Schram, Peter, M.D. Menninger Clinic 5800 SW Sixth Avenue PO Box 829 Topeka, KS 66601-0829	United States	497/018	2	3	5

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Seiden, Leslie M.D. Center for Research in Anxiety, Inc. 133 East 91st Street New York, New York 10128 *(Co-Investigator with JoAnne Santo, Ph.D.)* Santo, JoAnne, Ph.D. Center for Research in Anxiety, Inc. 133 East 91st Street New York, New York 10128 *(Co-Investigator with Leslie Seiden, M.D.)*	United States	497/019	7	8	15
Simpson, George M., M.D. LAC + USC Medical Center Psychiatric Outpatient Clinic 1937 Hospital Place Los Angeles, CA 90033	United States	497/020	0	1	1
Udelman, Harold D., P.C., M.D. 45 E. Osborn Road Phoenix, AZ 85012	United States	497/022	4	4	8
Zimbroff, Dan L., M.D. Behavioral Medicine Center Loma Linda University Med. Center 1710 Barton Road Redlands, CA 92373	United States	497/023	7	6	13
Kukha-Mohamad, S., M.D. 515-750 Spadina Cresent East Saskatoon, SK S7K 3H3	Canada	497/024	4	3	7
La Jeunesse, Charles, M.D. Management Pharmaco-Medical (MPM) 1134 Chemin St-Louis Sillery, Quebec G1S 1E5	Canada	497/025	2	3	5

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Morris, Paul, M.D. Toronto Centre for Behavioral Medicine Inc. 1243 Islington Ave. #608 Toronto, Ontario, Canada M8X 1Y9	Canada	497/026	2	0	2
Savard, Pierre, M.D., Ph.D. Hospital du Care-Coeur de Montreal 1575 Henri-Bourssa O. Montreal, Canada H3M 3A9	Canada	497/027	4	5	9
Turner, Peter G., M.D. Mood and Anxiety Disorders Clinic 3155 Harvester Rd., Suite 310 Burlington, Ontario L7N 3V2 *and* 30 Plains Road Burlington, Ontario L7T 2C6	Canada	497/028	7	8	15
Melchor, Pedro, M.D. 2348 N. 7th Street Miami, FL 33125 *and* Community Mental Health Center 1469 N.W. 36 St. Miami, FL 33142	United States	497/029	5	4	9

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Sokolski, Kenneth N., M.D. Affiliated Research Institute 801 N. Tustin Avenue, Suite 501 Santa Ana, CA 92705 *and* Dr. Rosenfeld's Office 24022 Calle De La Plata Suite 540 Laguna Hills, CA 92653	United States	497/031	4	4	8

SmithKline Beecham
Pharmaceuticals

ORIGINAL

October 7, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 08 1998
RECEIVED HFD-120
ORIG AMENDMENT
N (BB)

FDA Request for Information

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for treatment of panic disorder. Reference is also made to the request by the biopharm reviewer, Dr. Rae Yuan, for additional information regarding a bioavailability study submitted in NDA 20-982.

Submitted herein, per Dr. Yuan's request, are diskettes containing individual patient plasma concentration data for bioequivalence study 29060/569 submitted in the aforementioned NDA. Please note the EXCEL file contains four worksheets; CIDRA DOSE 1, CIDRA DOSE 2, CRAWLEY DOSE 1 and CRAWLEY DOSE 2. These correspond to Tables B.1 to B.4, respectively, in Appendix B of the study report, where explanatory footnotes for *flagged* data in the EXCEL file can be found.

Should you have any questions, or need any additional information, please do not hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

ORIGINAL

July 2, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 06 1998
RECEIVED HFD-120

FDA Request for Information

~~ORIG~~ AMENDMENT
N (BM)

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for treatment of panic disorder. Reference is also made to the June 19, 1998 fax from the Division's medical reviewers requesting additional information regarding this application.

Submitted herein, in duplicate, are SB's responses to the aformentioned request. For your convenience, each question is duplicated in Attachment 1 and is followed by the respective response. Attachments 2 and 3 contain the adverse event thesaurus sorted by verbatim and preferred terms respectively; Attachment 4 contains the relative risk data tables and, finally, hardcopy printouts of the requested P-values are provided in Attachment 5.

Should you have any questions, or need any additional information, please do not hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

ORIGINAL

June 30, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

FDA Request for Information: SAS Datasets

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for panic disorder. Reference is also made to the June 3, 1998 Fax from the statistical reviewer Sue-Jane Wang, Ph.D. requesting SAS datasets and other information regarding this application.

Submitted herein, per Dr. Wang's request, are diskettes containing the SAS transport files for the primary and secondary efficacy variables for each of the three principal studies, 494, 495 and 497. Two copies are provided for the NDA file and a third set is provided as a desk copy for Dr. Wang. Please refer to the enclosed instructions on downloading the respective files.

In addition to the diskettes provided in Attachment 1, descriptions of the datasets are provided in Attachment 2; the first 20 observations from studies 494, 495 and 497 are provided in Attachments 3 –5 respectively; Attachment 6 contains the requested annotated CRF containing the variable names used in the data files; and Attachment 7 contains the "Reporting and Analysis Plan" describing the algorithms used for derivation of the various datasets.

Regarding a hardcopy of the program, please note that since this consists of approximately 15,000 pages, a hardcopy is not provided in this submission. The code

for the efficacy parameters are contained within the ".SAS" files. There is one program for each variable, i.e. 10 efficacy source code files for each study, and are listed on page 000006.

Finally, as we discussed at our teleconference, a table of contents for the case report forms submitted in the NDA were provided electronically to the Division as "N0290936\CRF\CRFTOC.PDF".

Should you have any questions, or need any additional information, please don't hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

FAX'd 6/19/98

MEMORANDUM

TO: SmithKline Beecham Pharmaceuticals
ATTN: Thomas F. Kline
Manager, U.S. Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, Pennsylvania 19426

FROM: Food and Drug Administration
Center for Drug Evaluation and Research/ORM/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

DATE: June 19, 1998

SUBJECT: NDA 20-982
Request for Information

We request that you respond to the following items in order to assist us in reviewing your New Drug Application for Paxil CR in the treatment of panic disorder.

1) We note some large differences between the sizes of the intent-to-treat populations for studies 494, 495, and 497 as displayed in Table 3 of the ISE (vol. 1.31, page 44) and the N's shown for the endpoint (LOCF) efficacy analyses in the study reports, with the former being larger than the latter. For example, in considering the LOCF N's for mean change from baseline in the number of full panic attacks in the Paxil CR treatment group for studies 494 and 495 (vol. 1.8, page 106 and vol. 1.16, page 106, respectively), the following discrepancies are apparent:

	ITT N ISE Table 3	LOCF N Study Reports
Study 494	139	126
Study 495	158	139

It is unclear why the LOCF N's are much smaller than the ITT number of patients. Please explain these differences.

2) The protocols for studies 494, 495, and 497 indicate that the primary measure of efficacy would be the proportion of patients who attained zero panic attacks. However, the ISE now indicates that you are considering this variable as well as a) the mean change from baseline in the number of full panic attacks and b) the mean change from baseline in the CGI severity score as primary efficacy variables. Please provide your rationale for modifying the primary measures of efficacy.

3) For each primary and secondary efficacy variable, please provide the p-values for the drug/placebo comparisons at each assessment point during these studies for the observed cases datasets. For studies 494 and 495, this should include analyses that excluded center 33 and center 5, respectively.

4) Please provide a copy of the adverse event thesaurus that was used to code verbatim terms to preferred terms. We ask that this be done in two formats, one indexed by verbatim term and one by preferred term.

5) Please perform an analysis of the effects of demographic variables (age, gender, race) on the incidence of common and likely drug-related adverse events, i.e. those events reported in at least 5% of the Paxil CR patients and at a rate at least twice the placebo rate, within the pool of studies 494, 495, and 497. We ask that you use the following methodology; we have used gender as an example. For the identified adverse events, calculate the relative risks for male patients (RRm) and for female patients (RRf) with reference to placebo and compute the respective 95% confidence intervals within this study pool. Next, determine the ratios of the relative risks for females to males (RRf/RRm). Then, using the Mantel-Haenszel method, compute odds ratios for each subgroup and also a common odds ratio with the 95% confidence interval. Finally, test the homogeneity of the odds ratios between subgroups for each selected adverse event using the Breslow-Day Chi-Square and provide p-values. Please submit the results as shown in the two attached tables. Similar analyses should be carried out for age and race effects for these same adverse events.

Your timely response to these requests is very much appreciated. Should questions arise, please contact Dr. Dubitsky at (301)594-5543.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer
Psychiatric Drug Products Group

/S/

Thomas P. Laughren, M.D.
Group Leader
Psychiatric Drug Products Group

cc: HFD-120/GDubitsky
TLaughren
AHomonnay

Attachment: Two tables.

ATTACHMENT

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR SELECTED STUDY EVENTS

Adverse Events	MALES				FEMALES				RR = RRf ÷ RRm
	Paxil CR (n=) N (%)[3]	Placebo (n=) N (%)	RRm[1]	95% C.I.	Paxil CR (n=) N (%)	Placebo (n=) N(%)	RRf[2]	95% C.I.	

ODDS RATIOS BY GENDER FOR SELECTED ADVERSE EVENTS

Adverse Event	Odds Ratios[4]		Common Odds Ratio[5]	95% C.I.	Breslow-Day[6]	
	Males	Females			χ^2	p-value

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1 RRm = relative risk for male patients (Paxil CR/placebo).
2 RRf = relative risk for female patients (Paxil CR/placebo).
3 N = number of patients with the event and % = (N ÷ n) × 100%.
4 Odds ratios computed with reference to placebo patients.
5 Common odds ratio computed using the Mantel-Haenszel method.
6 Breslow-Day test for homogeneity of the odds ratios.

facsimile
TRANSMITTAL

To: Thomas Kline
Sponsor: SmithKline Beecham
Fax #: (610) 917-7665
Re: Electronic Data Requirements for Statistics
Date: 6/4/98
Pages: (including cover sheet) 3

From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug
Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

TO: Thomas Kline
Manager
U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals

FAX:

FROM: Sue-Jane Wang, Ph.D.
Mathematical Statistician
Division of Biometrics I, CDER, FDA

Date: June 3, 1998

RE: Electronic Data Request for NDA# 20-982: Paxil CR Tablets

Dear Mr. Kline,

Please submit the following for NDA#20-982 statistical review and evaluation:

1) Documentation of data files per protocol, including formats of coding and explanation of coding. When derived variables are used, please provide the algorithms used for derivation.

2) Annotated Case Report Form (CRF with variable names used in the SAS data files)

3) Listing of Case Report Form

Diskettes (1 diskette per trial), including

1) SAS macro files (Please include those files for your primary efficacy endpoint and for your secondary efficacy endpoints analyses).

2) Datasets

A). Please submit an electronic data file that includes
- Basic patients identification;
- Baseline AEDs therapy at screen;
- Relevant information for early discontinuation assessment: date of screen, date of randomization, early withdrawal (Y/N), date of withdrawal or date of trial completion, date last seen if different from date of withdrawal, reason of discontinuation;
- Demographic variables;
- Efficacy related information: baseline medical history, baseline measurements (individual items and total measurement if applicable), date of baseline measurements collected, final measurements (individual items and total measurement if applicable), date of final measurements collected for the primary and secondary efficacy variables, indicators of ITT, LOCF, OC, retrieved dropout analysis,

etc.
This file should contain one record per patient.

B). Please submit an electronic data file that includes raw data:
- Basic patients identification;
- For each visit, the primary and secondary efficacy measurements including date or week of each visit, visit #; etc.
- For each visit, the individual items (e.g., all panic attacks includes full panic attacks, full situational panic attacks, etc.) which constitute the primary and secondary efficacy variables. This file should contain one visit per record.

1) Hardcopy of program
2) Output of contents
3) Print out of first 20 obs.

Please provide each type of file separated by trials. The SAS system *.sd2 files or transport files *.xpt are fine.

Thank you.

SmithKline Beecham
Pharmaceuticals

ORIGINAL

May 27, 1998

Anna M. Homonnay-Weikel
Project Manager

Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Agency Request for Information

NCBM

Dear Anna,

Reference is made to NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

Submitted herein, in duplicate, is a list of investigators pertaining to the aforementioned application. As we discussed on the phone, a duplicate copy of this submission also has been sent to:

Dr. Robert Young
Food and Drug Administration
7520 Standish Place
Route 125
Rockville, Maryland 20855

Please do not hesitate to contact me at (610) 917-5970 should you have any questions or need any additional information.

Sincerely,

Thomas F. Kline
Manager
US Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707

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SB
SmithKline Beecham
Pharmaceuticals

DUPLICATE

May 20, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

...CORRESP

CENTER FOR DRUG EVALU
AND RESEARCH

MAY 2 2 1998

RECEIVED HFD.

General Correspondence: Electronic Files

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for the treatment of panic disorder.

Submitted herein, per the Divison's request, are CDs containing the aforementioned New Drug Application in PDF format. Also provided, for reviewer convenience, and as an optional installation, is a —— based review tool to assist the respective reviewers. If the Division chooses to utilize this review tool, SB would be glad to assist in its installation and provide individual reviewer training.

Please refer to page 000005 for a brief set of instructions regarding the PDF installation on your network. Should you have any questions, please don't hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

OCT - 6 199

000001

MEETING MINUTES

Date: June 16, 1998
NDA: 20-982
Location: Woodmont II, Conference Room E
Sponsor: SmithKline Beecham Pharmaceuticals
Drug: Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets
Indication: Panic Disorder
Meeting Type: 45 Day Filing Meeting
Participants:

Paul Leber, M.D.
Tom Laughren, M.D.
Greg Dubitsky, M.D.
Bob Seevers, Ph.D.
Rick Lostritto, Ph.D.
Sue Jane Wang, Ph.D.
Rae Yuan, Ph.D.
Anna M. Homonnay-Weikel, R.Ph. (Project Manager)
Alfreda Burnetta (DSI)

BACKGROUND:

SmithKline Beecham Pharmaceuticals has submitted an efficacy supplement for panic disorder. It has been assigned a new NDA number pending approval of NDA 20-936 for Paxil CR in the treatment of Depression (per the 'Bundling Policy). The application consists of three clinical studies and statistical analyses. The pharmacology/toxicology and chemistry, manufacturing, and controls sections reference previously submitted NDA 20-936 and approved NDA 20-031.

DISCUSSION:

CLINICAL

- The application appears to be fileable.

STATISTICAL

- The application appears to be fileable. The firm has submitted the requested datasets.

CONCLUSION:

The application appears on its face to be acceptable for filing.

Minutes prepared by: /S/
Anna M. Homonnay-Weikel, R.Ph.
Project Manager

cc: Orig NDA & Div File

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APPEARS THIS WAY
ON ORIGINAL